UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 08/908,884 | 08/08/1997 | XINNIAN DONG | 00786/339004 | 9977 |

21559 7590 08/31/2004

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| KUBELIK, ANNE R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1638 | |

DATE MAILED: 08/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/908,884 | DONG ET AL. | |
| | Examiner | Art Unit | |
| | Anne R. Kubelik | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-13,15-29,36,40-42 and 47-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-13,15-29,36,40-42 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 are pending. The office action mailed 14 November 2003, and Applicant's response, filed 18 May 2004, both indicated that claims 53-54 were present; however, a review of the record indicates that this is not the case.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 101*

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 36 and 49 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well-established utility.

Claims 36 and 49 are drawn to a method of producing an acquired resistance protein by culturing a cell transformed with a nucleic acid encoding such a protein and recovering the protein.

However, the only utility for such a protein proposed by the specification is to produce an antibody to the protein (pg 8, lines 19-22; pg 64, line 22, to pg 65, line 3; pg 68, line 16, to pg 69, line 6) and to isolate proteins that interact with the protein (pg 68, lines 1-15). The only utility proposed for the antibody is to monitor the level of the protein in a plant (pg 69, lines 4-6); no utility is given for that knowledge. There is no proposed utility for proteins that interact with NPR1. Thus, the asserted utility for the protein is not substantial.

The artisan would need to prepare, isolate and analyze the NPR1 protein to determine what utility, if any, it has. The artisan would also need to prepare, isolate and analyze antibodies to NPR1 or proteins that interact with NPR1 to determine what specific and substantial utility, if any, there is to monitoring the level of the protein in a plant or having interacting proteins.

It is apparent that extensive further research, not considered to be routine experimentation, would be required before one skilled in the art would know how to use the claimed invention. It has been established in the courts that a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form, there is insufficient justification for permitting an application to engross what may prove to be a broad field (*Brenner v. Manson,* 383 U.S. 519 (1966)).

Thus, it is unclear how one of ordinary skill in the art would be able to utilize the protein produced by the claimed method of producing the protein. Accordingly, the claimed invention lacks a "real-world" use.

### *Claim Rejections - 35 USC § 112*

5. Claims 36 and 49 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claims 47-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Neither the instant specification nor the originally filed claims appear to provide support for the phrase in claim 47, written to incorporate the language from claim 1, "An isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, wherein said acquired resistance polypeptide confers, on a plant expressing said polypeptide, resistance to a plant pathogen, wherein said nucleic acid complements an acquired resistance mutant." Similarly, neither the instant specification nor the originally filed claims appear to provide support for the phrase in claims 49 and 51, "wherein said nucleic acid complements an acquired resistance mutant", wherein the nucleic acid an isolated nucleic acid molecule encoding an acquired resistance polypeptide comprising an ankyrin repeat, or that hybridizes to a nucleic acid molecule comprising SEQ ID NOs:1, 2 or 13.

Thus, such phrases constitute NEW MATTER. In response to this rejection, Applicant is required to point to support for the phrase or to cancel the new matter.

7. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 November 2003. Applicant's arguments filed 18 May 2004 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that encode proteins with ankyrin repeats. In contrast, the specification only describes coding sequences from *Arabidopsis*

*thaliana* and *Nicotiana glutinosa* that comprise SEQ ID NOs:1, 2 and 13. Applicant does not describe other nucleic acids encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Furthermore, claim 6 is drawn to such a nucleic acid from any Cruciferae. Cruciferae comprises at least 162 genera, including Aethionema, Alliaria, Alyssum, Apophyllum, Arabidopsis; Arabis, Armoracia, Atamisquea, Aubrieta, Aurinia, Barbarea, Belencita, Beringia, Berteroa, Berteroella, Bivonaea, Boechera, Boleum, Boscia, Brassica, Braya, Buchholzia, Cadaba, Cakile, Calepina, Camelina, Capparis, Capsella, Cardamine, Cardaria, Carrichtera, Caulanthus, Cheesemania, Chorispora, Cleome, Cleomella, Cochlearia, Cochleariella, Coincya, Conringia, Coronopus, Crambe, Crambella, Crateva, Crucihimalaya, Cusickiella, Dactylaena, Dentaria, Descurainia, Dichasianthus, Dimorphocarpa, Diplotaxis, Dipterygium, Dithyrea, Draba, Drabopsis, Dryopetalon, Erophila, Eruca, Erucastrum, Erysimum, Euadenia, Eutrema, Euzomodendron, Forchhammeria, Fortuynia, Gagria, Guillenia, Guiraoa, Gynandropsis, Halimolobos, Hemicrambe, Hilliella, Hirschfeldia, Hornungia, Hymenolobus, Ianhedgea, Iberis, Ionopsidium, Isatis, Ischnocarpus, Isomeris, Iti, Jonopsidium, Kernera, Kremeriella, Leavenworthia, Lepidium, Lesquerella, Lobularia, Lunaria, Lyrocarpa, Maerua, Mancoa, Matthiola, Megacarpaea, Microthlaspi, Moricandia, Morisonia, Mostacillastrum, Muricaria, Nasturtium, Neobeckia, Neotorularia, Nerisyrenia, Nerisyrenia linearifolia, Neslia, Noccidium, Notothlaspi, Olimarabidopsis, Orychophragmus, Oxystylis, Pachycladon, Pachyphragma, Peltaria, Pennellia, Physaria, Physorhynchus, Podandrogyne, Polanisia, Polyctenium, Pringlea, Pritzelago, Pseudoarabidopsis, Psychine, Raphanus, Rapistrum, Rhizobotrya, Ritchiea, Romanschulzia, Rorippa, Savignya, Schivereckia, Schoenocrambe, Schouwia, Sibara, Sinapidendron, Sinapis,

Sisymbrium, Smelowskia, Sphaerocardamum, Stanleya, Steriphoma, Streptanthella, Streptanthus, Succowia, Synthlipsis, Teesdalia, Thellungiella, Thelypodiopsis, Thelypodium, Thlaspi, Thylachium, Thysanocarpus, Vania, Vella, Warea, Werdermannia, Wislizenia, Yinshania, and Zilla (see http:// www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi). These genera total thousands of species. For example, the genus *Arabidopsis* alone comprises at least 53 species: *A. arenosa, A. bactriana, A. brevicaulis, A. bursifolia , A. campestris, A. cebennensis, A. croatica, A. dentata, A. drassiana, A. erysimoides, A. eseptata, A. gamosepala, A. glauca, A. halleri, A. himalaica, A. huetii, A. kneuckeri, A. korshinskyi, A. lasiocarpa, A. lyrata, A. mollis, A. mollissima, A. mongolica, A. multicaulis, A. neglecta, A. novae-angliae, A. nuda, A. ovczinnikovii, A. parvula, A. pedemontana, A. petraea, A. petrogena, A. pinnatifida, A. pumila, A. qiranica, A. richardsonii, A. rupicola, A. russelliana, A. sarbalica, A. stenocarpa, A. stewartiana, A. suecica, A. taraxacifolia, A. tenuisiliqua, A. thaliana, A. tibetica, A. toxophylla, A. trichocarpa, A. tschuktschorum, A. tuemurnica, A. verna, A. virgata,* and *A. yadungensis* (see The International Plant Names Index, http://www.ipni.org/index.html). The specification describes only one NPR1 gene (SEQ ID NO:1) from only one of these species, *Arabidopsis thaliana.*

Claim 5 is drawn to such a nucleic acid from any *Solanaceae*. *Solanaceae* comprises at least 57 genera, including *Anisodus, Anthocercis, Anthotroche, Athenaea, Atropa, Aureliana, Brachistus, Browallia, Brunfelsia, Capsicum, Cestrum, Coeloneurum, Crenidium, Cuatresia, Cyphanthera, Datura, Deprea, Duboisia, Duckeodendron, Espadaea, Goetzea, Goetzia, Grabowskia, Grammosolen, Henoonia, Hyoscyamus, Jaborosa, Jaltomata, Juanulloa, Larnax, Lycianthes, Lycium, Mandragora, Metternichia, Nicandra, Nicotiana, Nierembergia, Nolana,*

*Normania, Petunia, Physalis, Salpiglossis, Saracha, Schizanthus, Schwenckia, Scopolia, Sessea, Solandra, Solanum, Lycopersicon, Symonanthus, Triguera, Tubocapsicum, Vassobia, Vestia, Withania,* and *Witheringia*. These genera total thousands of species (see http:// www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi). For example, the genus *Nicotiana* alone comprises at least 72 species: *N. acaulis, N. acuminata, N. africana, N. alata, N. amplexicaulis, N. arentsii, N. attenuata, N. benavidesii, N. benthamiana, N. bigelovii, N. bonariensis, N. bonavidesii, N. cavicola, N. clevelandii, N. cordifolia, N. corymbosa, N. debneyi, N. didepta, N. digluta, N. eastii, N. excelsior, N. exigua, N. forgetiana, N. fragrans, N. glauca, N. glutinosa, N. goodspeedii, N. gossei, N. hesperis, N. ingulba, N. kawakamii, N. knightiana, N. langsdorfii, N. linearis, N. longiflora, N. maritima, N. megalosiphon, N. miersii, N. nesophila, N. noctiflora, N. nudicaulis, N. obtusifolia, N. occidentalis, N. otophora, N. palmeri, N. paniculata, N. pauciflora, N. petunioides, N. picilla, N. plumbaginifolia, N. quadrivalvis, N. raimondii, N. repanda, N. rosulata, N. rotundifolia, N. rustica, N. setchellii, N. simulans, N. solanifolia, N. spegazzinii, N. stocktonii, N. suaveolens, N. sylvestris, N. tabacum, N. thyrsiflora, N. tomentosa, N. tomentosiformis, N. trigonophylla, N. umbratica, N. undulata, N. velutina,* and *N. wigandioides*. The specification describes only one possible NPR1 gene (SEQ ID NO:13) from only one of these species, *Nicotiana glutinosa*.

The specification does not describe all the necessary and sufficient structural motifs that distinguish nucleic acids that encode ankyrin-repeat containing proteins that do confer disease resistance upon a plant from nucleic acids that encode ankyrin-repeat containing proteins that do not confer disease resistance upon a plant. Ankyrin repeats comprise less than 10% of the total length of the proteins encoded by the claimed nucleic acids and those ankyrin repeats are present

in a great number of other proteins that did not have AR activity. Sedgwick et al (1999, Trends Biochem. Sci. 24:311-316) teach the ankyrin repeats are found in a wide range of proteins, including inhibitors, developmental regulators, cytoskeleton organizers and toxins and that in most of these proteins ankyrin repeats are combined with unrelated structural modules (pg 311, column 3, paragraph 1). Ankyrin repeats appear to be involved in protein-protein interactions and not in the unique role of the protein (Sedgwick et al, paragraph spanning pg 311-312, and Cao et al, 1997, Cell 88:57-63, pg 61, left column, paragraph 3[1]). What are the common structural features of the non-ankyrin repeats portion of the proteins encoded by the claimed nucleic acids?

Hence, Applicant has not, in fact, described nucleic acids that encode proteins with ankyrin repeats within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant urges that *Lilly* makes clear that written description of a genus of DNA may be achieved by recitation of structural features common to members of a genus, and they have described the claimed class of acquired resistance genes and their shared ankyrin repeats; and have provided evidence, by way of WO 00/70069, that those skilled in the art also recognized the ankyrin motif as a structural characteristic common to members of the genus (response pg 9-10).

---

[1] The first author of this paper is one of the instant inventors, Hui Cao.

This is not found persuasive. WO 00/70069 also states that the NPR1 protein has nuclear localization signals, phosphorylation sites, and homology with IFκB (pg 3, lines 8-13), thus recognizing that other features are also essential structural characteristics. Furthermore, the function of NPR1 requires more than the ankyrin repeats. Kinkema et al (2000, Plant Cell 12:2339-2350)[2] teach that nuclear localization is required for activation of PR gene expression by NPR1; mutation in the nuclear localization signals located at the C-terminal end of NPR1 prevents its nuclear location and thus, activation of PR-1 expression (Fig. 3B, pg 2344, right column, paragraph 2, to pg 2345, right column, paragraph 1). Ryals et al (1997, Plant Cell 9:425-439) teach that $Arg^{432}$ is critical for function (Table 3). Aravind et al (1999, J. Mol. Biol. 285:1353-1361) teach that NPR1 has a POZ domain, which is involved in protein-protein interaction, spanning amino acids 62-176 (Fig. 1); Fan et al (2002, Biology of Plant-Microbe Interactions 3:94-98)[3] demonstrated its importance in induction of PR gene expression (paragraph spanning pg 95-96). Thus, a description of a nucleic acid encoding an NPR1 protein must include at least these structural features.

Applicant urges that their "own mutational analysis demonstrated that disruption of the ankyrin consensus ... rendered plants susceptible to disease; evidencing the ankyrin motif ... as structurally and functionally defining" (response pg 10).

This is not found persuasive because Applicant's own mutational analysis contradicts this statement. The npr1-2 mutation occurs outside any ankyrin repeat (specification, pg 47); thus, even Applicant's results show that more than the ankyrin repeats are required for the function of

[2] One of the authors of this paper is one of the instant inventors, Xinnian Dong.
[3] One of the authors of this paper is one of the instant inventors, Xinnian Dong.

conferring disease resistance. Thus, the structural description of encoding an ankyrin repeat is not coextensive with function, and Applicant's description is incomplete.

The ankyrin repeats total about 55 amino acids, while the total length of NPR1 proteins is about 590 amino acids (SEQ ID NO:3 is 593 amino acids long and the putative NPR1 protein from *Nicotiana* is 588 amino acids long). Thus, ankyrin repeats comprise less than 10% of the total protein length. What are the structural features of the rest of the claimed nucleic acids? Furthermore, the specification does not describe the structural and functional features of the nucleic acids that encode ankyrin-repeat-containing disease resistance proteins that distinguish them from ankyrin-repeat-containing proteins that are not disease resistance proteins. What are the structural features that indicate that a given ankyrin protein-encoding nucleic acid encodes a protein that plays a role in disease resistance? The specification does not describe these; thus Applicant was not in possession of the claimed genus.

Applicant urges, with respect to claims 5-6, that the specification need not precisely describe all subject matter claimed, merely that the inventor was in possession of the invention at the time of filing; the claimed cruciferous and solanaceous resistance genes have been described, as one of skill in the art would recognize (response pg 10-11).

This is not found persuasive. One of skill in the art would know that Applicant was not is possession of the claimed cruciferous and solanaceous resistance genes because the structural features of the genes was not disclosed. It is noted that even today, 8 years after filing, only a few of the thousands cruciferous and solanaceous NPR1 genes have been cloned and the structural features described.

Applicant urges that the reliance on Shokal is misplaced because the Office takes the position that in order to support the broad language found in the claim, the specification must be equally broad in naming, and using in examples, the representative specifies encompassed by the claim language. Applicant urges that because the specification describes in clear language the claimed invention but also describes relevant identifying characteristics of the claimed invention, Shokal is not applicable. Applicant urges that in Shokal the generic claim was not disclosed in the specification and exemplary species were relied on to illustrate and define the genus (response pg 12-13).

This is not found persuasive. The specification does not describe the invention within the full scope of the claims, nor does it describe the relevant identifying characteristics of the claimed invention. The structural description "encoding a protein comprising an ankyrin repeat" is not sufficient.

The specification in describing one, or potentially two nucleic acids, that fall within the scope of the claims does not describe a representative number of nucleic acids within that scope, given the thousands and thousands of plants species and given that Applicant recites only one common structural feature that is also present in a vast number of non-NPR1-proteins.

8. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for NPR1 coding sequences from Arabidopsis that comprise SEQ ID NOs:1 and 2, does not reasonably provide enablement for any nucleic acid that encodes an ankyrin-repeat-containing disease resistance protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these

claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 November 2003. Applicant's arguments filed 18 May 2004 have been fully considered but they are not persuasive.

With respect to claims 36 and 49, this scope of enablement rejection is made in the event that Applicant is able to overcome the utility and enablement rejections as set forth above.

The claims are broadly drawn to a multitude of nucleic acids that encode ankyrin-repeat-containing proteins.

The instant specification, however, only provides guidance for isolation of the Arabidopsis *nprl-l, 1-2*, and *1-3* mutants, which have a block in induction of SAR did not inhibit the growth of avirulent pathogens, and have reduced expression of PR genes (pg 21-23 and 24-32), map-based cloning of the NPR1 gene, SEQ ID NO:1 (pg 23 and 33-35), complementation of the nprl mutants (pg 35-41), isolation of an NPR1 cDNA, SEQ ID NO:2, which encodes SEQ ID NO:3 (pg 43-44), transformation of wild-type *Arabidopsis* with SEQ ID NO:2 expressed from the CaMV 35S promoter to show that plants that overexpressed the protein had increased resistance to bacterial and fungal pathogens (pg 44-46), a demonstration that NPR1 is translocated to the nucleus (pg 46-47), characterization of the *nprl* mutations (pg 47-48), and isolation of a *Nicotiana glutinosa* cDNA (SEQ ID NO:13) by hybridization with SEQ ID NO:2 (pg 49-50).

The instant specification fails to provide guidance for nucleic acids other than SEQ ID NOs: 1, 2 and 13 that encode ankyrin-repeat-containing proteins.

The presence of an ankyrin repeat does not mean a protein plays a role in plant disease resistance. Sedgwick et al (1999, Trends Biochem. Sci. 24:31 1-316) teach the ankyrin repeats

are found in a wide range of proteins, including inhibitors, developmental regulators, cytoskeleton organizers, and toxins and that in most of these proteins, ankyrin repeats are combined with unrelated structural modules (pg 31 1, column 3, paragraph 1). Ankyrin repeats appear to be involved in protein-protein interactions and not in the unique role of the protein (Sedgwick et al, paragraph spanning pg 311-312, and Cao et al, 1997, Cell 88:57-63, pg 61, left column, paragraph 3[4]).

The function of NPR1 requires more than the ankyrin repeats. The specification teaches that NPR1 is localized to the nucleus (pg 46-47). Kinkema et al (2000, Plant Cell 12:2339-2350)[5] teach that nuclear localization is required for activation of PR gene expression by NPR1; mutation in the nuclear localization signals located at the C-terminal end of NPR1 prevents its nuclear location and thus, activation of PR-1 expression (Fig. 3B, pg 2344, right column, paragraph 2, to pg 2345, right column, paragraph 1). The claims are not directed to proteins with this motif.

Additionally, other amino acids are critical for NPR1 function. Ryals et al (1997, Plant Cell 9:425-439) teach that $Arg^{432}$ is critical for function (Table 3). The specification does not teach the requirement for this amino acid.

Aravind et al (1999, J. Mol. Biol. 285:1353-1361) teach that NPR1 has a POZ domain, which is involved in protein-protein interaction, spanning amino acids 62-176 (Fig. 1); Fan et al (2002, Biology of Plant-Microbe Interactions 3:94-98)[6] demonstrated its importance in induction of PR gene expression (paragraph spanning pg 95-96). The specification does not teach this domain and the claims are not directed to a nucleic acid encoding a protein with this domain.

---

[4] The first author of this paper is one of the instant inventors, Hui Cao.

Thus, the specification does not teach all the necessary and sufficient structural motifs that would enable one to distinguish nucleic acids that encode ankyrin-repeat containing proteins that do confer disease resistance upon a plant from nucleic acids that encode ankyrin-repeat containing proteins that do not confer disease resistance upon a plant.

The specification fails to provide evidence that the *N. glutinosa* nucleic acid SEQ ID NO:13 encodes a protein that confers disease resistance to a plant expressing the protein and has a functional relatedness to the *Arabidopsis* NPRI gene.

The specification does not teach any nucleic acid, other than SEQ ID NOs:1 and 2, that are able to complement any acquired resistance mutant, including any *Arabidopsis npr* mutant. Even SEQ ID NO:13 has not been shown to complement any of these mutants, and it is not clear that it would be able to do so.

As the specification does not describe the transformation of any plant with any ankyrin-repeat-containing protein encoding nucleic acids other than SEQ ID NO:1 and 2, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encoding ankyrin-repeat containing proteins and plants transformed therewith, to identify those with enhanced disease resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

---

[5] One of the authors of this paper is one of the instant inventors, Xinnian Dong.
[6] One of the authors of this paper is one of the instant inventors, Xinnian Dong.

Applicant urges that one of skill in the art using routine experimentation could easily identify and test the function of nucleic acids falling within Applicant's claims, and that no evidence has been provided by the Office to refute this assertion (response pg 14).

This is not found persuasive. The instant specification teaches that AR genes from other plants can be isolated by hybridization using all or part of the NPR1 cDNA as a probe or using all or part of the amino acid sequence to design AR-specific oligonucleotide probes or primers (pg 50-53). Famodu et al (WO 00/28036), however, did not follow the guidance of the instant specification to isolate NPR1 genes from corn, rice and wheat, but instead produced cDNA libraries from these plants, sequenced clones randomly, did a BLAST search on the sequence and found similarity to Arabidopsis NPR1 (pg 16). Bougri et al (WO 00/70069) also did not follow the guidance of the instant specification to isolate NPR1 genes from corn, rice and wheat, but instead used BLAST searches, and RT-PCR using primers based on the corn and Arabidopsis sequences (pg 27-31). Given "the low level of shared nucleotide and predicted protein identity" between SEQ ID NOs:2 and 3 and the rice, corn and wheat sequences (quote from Bougri et al, pg 32, lines 11-20; see also Famodu et al, pg 17), using Applicant's methods to isolate the rice, wheat and maize genes would require undue experimentation, if isolation by such methods were even possible. If one of skill in the art has to use different method steps to get the isolate the DNA to work, then the provided method of isolating it is not enabled.

Applicant urges that the Ausubel Declaration on pg 5 that nucleic acids falling within the scope of the claims can be identified and isolated routinely, and that no evidence has been made of record refuting this (response pg 14-15).

This is not found persuasive. That no one used Applicant's methods to isolate the claimed genes provides evidence that the guidance of the specification is insufficient.

See *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997), which teaches that disclosure of a "mere germ of an idea does not constitute [an] enabling disclosure", and that "the specification, not the knowledge of one skilled in the art" must supply the enabling aspects of the invention.

Applicant urges that the Office has provided no scientifically acceptable evidence or reason for doubting Applicant's statements, evidence or reasoning, as supported by the Dong and Ausubel declaration (response pg 15-16).

This is not found persuasive. That no one used Applicant's methods to isolate the claimed genes provides evidence that the guidance of the specification is insufficient.

Applicant urges that in contrast to *Genentech*, where the specification fails to disclose a useful conjugate or method for its cleavage, the instant specification provides the requisite starting materials (response pg 16-17).

This is not found persuasive. The requisite starting materials are provided in both; the instant specification provides the sequence of the *Arabidopsis* NPR1 gene, while Genentech provided the sequence of the human hGH gene. The exact hybridization and or amplification conditions for isolation of the full scope of claimed nucleic acids are not described in the instant specification. The instant specification teaches that AR genes from other plants can be isolated by hybridization using all or part of the NPR1 cDNA as a probe or using all or part of the amino acid sequence to design AR-specific oligonucleotide probes or primers (pg 50-53). Neither Famodu et al nor Bougri et al followed, or would have been able to follow, the guidance of the

instant specification to isolate NPR1 genes from corn, rice and wheat. If one of skill in the art has to use different method steps to get the method to work, then the method is not enabled.

Applicant urges that their reliance on *Ex Parte Chen* is to emphasize that the Office has not offered any evidence that the instantly claimed invention would require undue experimentation to practice (response pg 17).

This is not found persuasive. *Ex Parte Chen* is not comparable to the instant case. In *Ex Parte Chen*, the question was whether a method of transformation using a gene of known sequence was enabled. In the instant case the sequence of the gene is not known, thus plants transformed with the gene are not enabled. The claims are not enabled because the specification does not teach the structural features of the claimed genes. No one who as subsequently isolated NPR1 genes has used the hybridization and/or amplification conditions suggested by the instant specification, providing evidence that the instantly claimed invention would require undue experimentation to practice.

Applicant urges that their work stimulated Famodu et al to identify several NPR1 genes from corn, rice and wheat using the *Arabidopsis* NPR1 gene (response pg 17).

This is not found persuasive. Famodu et al did not use the guidance in the instant specification to isolate NPR1 genes from corn, rice and wheat, as discussed above. If one of skill in the art has to use different method steps to get the method to work, then the method is not enabled.

Furthermore, the specification does not teach the structural and functional features of the nucleic acids that encode ankyrin-repeat-containing disease resistance proteins that distinguish them from ankyrin-repeat-containing proteins that are not disease resistance proteins.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 10-13, 15-29, 36, 40-42 and 47-52 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is modified from the rejection set forth in the Office action mailed 14 November 2003, as applied to claims. Applicant's arguments filed 18 May 2004 have been fully considered but they are not persuasive.

Claims 10-12 17, 22, 36 and 40 are indefinite in their recitation of "hybridizes". The hybridization conditions are not defined; thus it is unclear which nucleic acids fall within the claims.

Applicant urges that the term is a clear and definite term known to the skilled artisan, and defined in examples on pg 12, 49 and 51 of the specification (response pg 18-19).

This is not found persuasive because examples do not define a term, and other definitions are possible.

In claim 28, it is unclear if the seed comprises the nucleic acid or vector.

Applicant urges that the claim has been amended to indicate that the seed is produced by the plant of claim 22 (response pg ).

This is not found persuasive because not all seeds of the plant of claim 22 will comprise the nucleic acid or vector.

Claim 50 is indefinite for being dependent upon a cancelled claim.

***Claim Rejections - 35 USC § 102***

11. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain rejected under 35 U.S.C. 102(e) as being anticipated by Ryals et al (US Patent 6,09 1,004, filed June, 1996).

Applicant urges that they believe they are the first to invent the claimed subject matter and that an interference should be declared (response pg 19).

This is not found persuasive. An interference cannot be declared until all other issues in the case are resolved. Additionally, Applicant must request an interference under 37 CFR 1.607 and make a showing under 37 CFR 1.608(a). See MPEP 2307 and 2308.

12. Claims 1-2, 4, 6-13, 15-25, 28-29, 36 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (1992, Plant Cell 4:1575-1588) in light of Applicant's response filed 18 May 2004.

Zhang et al teach a nucleic acid from *Arabidopsis* that encodes a protein with 4 ankyrin repeats (Fig. 1); both the cDNA and genomic clone were obtained (pg 1576, right column, paragraph 2). Zhang et al also teach expression vectors comprising the nucleic acid (Fig. 4) and *Arabidopsis* plants transformed with them via *Agrobacterium*-mediated transformation (pg 1578, right column, paragraph 2, to pg 1579, left column paragraph 2).

Applicant's response filed 18 May 2004 states "disruption of the ankyrin consensus ... rendered plants susceptible to disease; evidencing the ankyrin motif ... as structurally and functionally defining" (response pg 10). According to Applicant's statement, the ankyrin motif of Zhang et al defines the protein as an acquired resistance polypeptide; therefore, the plants produced by Zhang et al would inherently be resistant to plant pathogens, including bacteria,

viruses, viroids, fungi, nematodes and insects. The protein would also activate the expression of a pathogenesis-related protein. The nucleic acid taught by Zhang et al would also hybridize to SEQ ID NOs: 1, 2 and 13 under at least some hybridization conditions.

### *Double Patenting*

13. Claims 1-2, 4-13, 15-29, 36, 40-42 and 47-52 remain provisionally rejected under the judicially created doctrine of double patenting over claims 1-25 of copending Application No. 09/908,323. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 November 2003, as applied to claims. Applicant's arguments filed 18 May 2004 have been fully considered but they are not persuasive.

Applicant urges that a terminal disclaimer will be filed when allowable subject matter is determined (response pg 27). This is acknowledged.

### *Conclusion*

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Anne R. Kubelik, Ph.D.
August 26, 2004

ANNE KUBELIK
PATENT EXAMINER